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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/487,992	06/07/95	HALLENBECK	P 1136.0020001

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EXAMINER

TWOMEY, P

ART UNIT	PAPER NUMBER
1804	12

DATE MAILED: 12/18/96

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

See the attached.

Office Action Summary

Application No. 08/487,992	Applicant(s) Hallenbeck, et al.
Examiner Patrick Twomey	Group Art Unit 1804



Responsive to communication(s) filed on _____.

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1-40 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-40 is/are rejected.

Claim(s) 5, 10, and 11 is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 8-11

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Part III DETAILED ACTION

1. Claims 1-40 are pending. The construction and use of replication-defective viruses is contemplated.

Drawings

2. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

3. Claim 5 is objected to as being confusing. Claim 5 refers to the method of claim 4, however claim 4 is not drawn to method. For the purposes of examination, it will be assumed that claim 5 refers to the vector of claim 4.

4. Claims 10 and 11 are objected to as being confusing. Claims 10 and 11 refer to the vector of claim 9, however, claim 9 is drawn to a method using a vector. For the purposes of examination, it will be assumed that the vector of claims 10 and 11 is the vector described in claim 9.

Claim Rejections - 35 USC § 112

5. Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. Claims 1-40 are drawn to vectors capable of tissue-specific replication wherein a gene essential for replication is regulated

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by a tissue-specific promotor, cells which produce the virions and methods of using them. However, the specification does not enable any tissue specific vectors. The specification describes the production of plasmids which are expected to produce adenoviruses comprising tissue-specific promotors. The specification does not enable the production of these plasmids, however, because information vital to their production has not been included in the specification. For example, the manufacture of plasmids pAVS21.TK1 and SE280-E1, which are fundamental to the construction of the other plasmids, are described only by the improper incorporation of references to other, pending, patent applications which are not identified by any serial number.

7. The incorporation of essential material by reference to a pending application in which the issue fee has not been paid is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). See MPEP 6.08.01(p).

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8. The attempt to incorporate subject matter into this application by reference to the applications by Chiang and Kayden is improper because the issue fee has not been paid in either application. In addition, the Patent Application Location Monitoring system has no record of an application by Kayden with the referenced filing date.

9. Furthermore, the vector virions are to be produced by co-infection with a fragment of Add1327, however no information is given as to what this is, how it may be made or where it may be obtained. In addition, reference is made to figure 1 which is supposed to describe vectors pAVS21.TK1, pAVE1a02i and SE280-E1, however none of these plasmids appear on figure 1. Without this information none of the vectors exemplified in the specification can be made, nor does the specification provide adequate guidance as to how to construct any viruses other than adenoviruses.

10. In addition, the field of gene regulation is recognized as highly experimental and unpredictable. Dillon (applicant's reference AR2) reviewed attempts to use tissue-specific promotors in gene therapy and concluded:

These and other recent studies show that therapeutic genes can be delivered into target tissues with varying efficiency, but they also demonstrate that controlled expression of the gene remains a problem and that a considerable degree of optimization will be required in

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order to achieve therapeutic levels of gene expression in the appropriate tissues. Achieving reproducible expression is likely to be particularly important if a treatment is to be used on human patients (page 167 col 2 lines 28-36).

11. In addition, a panel appointed by the National Institutes of Health recently reviewed the state of gene therapy and concluded that (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995):

In part because gene regulation questions are unanswered, determining the appropriate dosage levels for viral vectors presents another major challenge (page 38 lines 1-2).

12. These quotes clearly show the experimental and unpredictable nature of gene expression technologies. Neither the specification nor the art provide examples to the artisan of viruses in which the promotors which regulate viral replication have been removed and replaced by tissue specific promotors. Without guidance from the specification or the art concerning the details of promotor and enhancer gene sequences, a person skilled in the art of recombinant viruses would be unable to make the claimed vectors with a reasonable expectation of success without undue experimentation.

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13. Claims 9 and 12-18 are drawn to a method of distributing a polynucleotide in a tissue *in vivo* using a vector which can only replicate in certain tissues as determined by the choice of promotor inserted into the plasmid. Further limitations include the use of Herpesvirus, Papovavirus, Papillomavirus and Hepatitis virus, and tumor-specific expression.

14. However, as described above, the specification does not provide adequate guidance to make such viruses. In addition, the specification does not provide guidance in how to use these viruses *in vivo*. The art of gene therapy is recognized as highly complex and experimental. The NIH report says further:

While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host (page 1 lines 16-23).

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15. In addition, Pennisi (Science 274:342-343, 1996), reporting recently on clinical trials with a similar replication-defective adenovirus, says:

And other researchers point out that the mice the McCormick team used to test the virus's anti-tumor effects may not be a good model of human patients. For one thing, the animals lacked immune systems, and therefore the studies could not address whether the body's immune system will get in the way of any therapeutic effects. Most adults have already been infected with adenoviruses, Klausner points out, and as a result they have immune systems that are primed to destroy the virus, possibly before it has a chance to spread throughout a tumor. Inactivation of the virus by the immune system has hindered efforts to use adenovirus in gene therapy, for example. "That's been a real problem," McCormick admits (page 343 col 1 line 9 to col 2 line 5).

16. Pennisi goes on to report that other similar adenoviral mutants have been able to replicate in normal cells with functional p53, whereas other mutants failed to grow in cervical cancer cells lacking p53. "These somewhat contradictory findings suggest 'the story is much more complicated' than the ONYX

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researchers think, says Berk, and that the virus may not be as effective or as discriminating as they hope." This shows that the use of tissue-specific replication-defective viruses *in vivo* is highly experimental and unpredictable. Neither the specification nor the art at the time of filing provide adequate guidance to the artisan in the use of these vectors to distribute a polynucleotide in a tissue *in vivo*. Art-recognized difficulties such as levels of expression, tissue specificity and anti-viral immune responses have not been adequately addressed. Without such guidance, a person skilled in the art would not be able to use these vectors in the claimed method with a reasonable expectation of success without undue experimentation.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 2, 10, 19, 20, 22, 29-31, 33, 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Ringold, et al. (Proc. Natl. Acad Sci. USA 74:2879-2883, 1977).

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19. Claims 1, 2, 10, 19, 20, 22, 29-31, 33, 40 are drawn to a vector capable of tissue-specific replication comprising a tissue-specific promotor operably linked to the coding region of the vector, a method of distributing a polynucleotide in cells using this vector, and also to cells containing this vector and a method of producing it.

20. Ringold describes experiments on mouse mammary tumor virus, a virus which grows in the mammary glands of mice and is known to cause mammary tumors. Ringold describes producing the virus by culturing GR mammary tumor cells (page 2879 col 2 lines 9-10), infecting hepatic tumor cells (HTC) and S49 lymphoma cells with the virus, and shows that the viral replication (as measured by production of viral RNA) is tissue-specific because it can be stimulated in GR tumor cells and HTC cells (tables 1 and 2, respectively) but not in S49 cells (table 3).

21. MMTV is an ecotropic murine RNA tumor virus which is produced by the mammary glands of mice in response to glucocorticoid and passed on from generation to generation in the mother's milk. Therefore, it is inherently capable of distributing a polynucleotide (its genome) in a tissue (mammary tissue) *in vivo* (in mice).

22. Claims 8, 27, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Gunzburg, et al. (*Virology* 155:, 236-248, 1986).

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23. Claims 8, 27, and 38 are drawn to a viral vector comprising a tissue specific promotor and a heterologous coding sequence and cells which produce the vectors.

24. Gunzburg discloses a viral vector based on mouse mammary tumor virus in which the env gene has been removed and replaced with the gene for neomycin phosphotransferase. MMTV is a virus with tissue-specific replication (page 238 col 1 lines 18-20). The virus was produced by culturing infected packaging cells and then infected tissues in vitro and produced NPT (page 239 line 1 to page 240 col 2 line 14).

25. Claims 4-7, 23-26 and 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by McCormick (WO 94/18992).

26. Claims 4-7 are drawn to an adenovirus in which the Ela coding region is under the control of a tissue-specific regulatory sequence.

27. McCormick discloses an adenovirus in which the Ela coding region is under the control of a tissue-specific regulatory sequence which allows replication only in tissues lacking a functional p53 (see abstract).

28. Claims 23-26 and 34-37 are drawn to cells containing an adenovirus in which the Ela coding region is under the control of a tissue-specific regulatory sequence.

29. McCormick discloses cells containing an adenovirus in which the Ela coding region is under the control of a tissue-specific

regulatory sequence which allows replication only in tissues lacking a functional p53 (page 31 lines 14-22).

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gunzburg et al. (Virology 155:236-248, 1986) in view of Culver, et al. (Science 256:1550-1552, 1992).

32. Claim 28 is drawn to a cell containing a tissue-specific vector which encodes a heterologous product which provides anti-tumor activity to the cells.

33. Gunzburg discloses cells which contain a tissue-specific vector which encodes a heterologous product. However, neomycin phosphotransferase is not known to have anti-tumor properties.

34. Culver discloses cells which produce retroviruses encoding thymidine kinase, a protein which produces an anti-tumor effect when the cells are treated with gancyclovir. Though Culver does not teach the use of vectors which only replicate in certain tissues, he does teach the utility of tissue-specificity in tumor

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therapy when he points out that vectors only infect tumor tissues and not non-dividing neural tissue. Therefore, it would be obvious to a person skilled in the art of viral gene therapy to use the tissue-specific vectors of Gunzburg to transfect the anti-tumor genes of Culver into cells.

35. Claims 3, 9, 11-18, 21, and 32 are free of the art. The art at the time of filing did not provide an enabling disclosure as to how to make and use recombinant DNA tumor viruses in which regulatory sequences of replication genes were replaced with heterologous tissue-specific promotors or for their use in gene therapy.

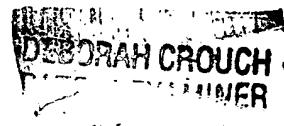
36. All claims are rejected. ~~~~~~

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick Twomey, Ph.D. whose telephone number is (703) 305-7022. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

38. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached on (703) 308-3153. The fax phone number for this Group is (703) 308-0294.

39. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Patrick Twomey, Ph.D.
December 11, 1996



Deborah Crouch
PATENT EXAMINER
GROUP 1800